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Description of the Related Art

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The design of synthetic ligands that read the information stored in the DNA double helix has been a long standing goal of chemistry. Cell-permeable small molecules which target predetermined DNA sequences are useful for the regulation of gene-expression. Oligodeoxynucleotides that recognize the major groove of double-helical DNA via triple-helix formation bind to a broad range of sequences with high affinity and specificity. Although oligonucleotides and their analogs have been shown to interfere with gene expression, the triple helix approach is limited to purine tracks and suffers from poor cellular uptake. The development of pairing rules for minor groove binding polyamides derived from N-methylpyrrole (Py) and N-methylimidazole (Im) amino acids provides another code to control sequence specificity. An Im/Py pair distinguishes G•C from C•G and both of these from A•T or T•A base pairs. Wade, W.S., Mrksich, M. & Dervan, P.B. describes the design of peptides that bind in the minor groove of DNA at 5'-(A,T)G(A,T)C(A,T)-3' sequences by a dimeric side-by-side motif. *J. Am. Chem. Soc.* **114**, 8783-8794 (1992); Mrksich, M. *et al.* describes antiparallel side-by-side motif for sequence specific-recognition in the minor groove of DNA by the designed peptide 1-methylimidazole-2-carboxamidenetropsin. *Proc. Natl. Acad. Sci. USA* **89**, 7586-7590 (1992); Trauger, J.W., Baird, E. E. Dervan, P.B. describes the recognition of DNA by designed ligands at subnanomolar concentrations. *Nature* **382**, 559-561 (1996). A Py/Py pair specifies A•T from G•C but does not distinguish A•T from T•A. Pelton, J.G. & Wemmer, D.E. describes the structural characterization of a 2-1 distamycin A-d(CGCAAATTTGGC) (SEQ ID NO: 1) complex by two-dimensional NMR. *Pro. Natl. Acad. Sci. USA* **86**, 5723-5727 (1989); White, S., Baird, E. E. Dervan, P.B. Describes the effect of the A•T/T•A degeneracy of pyrrole-imidazole polyamide recognition in the minor groove of DNA. *Biochemistry* **35**, 12532-12537

(1996); White, S., Baird, E. E. & Dervan, P.B. describes the pairing rules for recognition in the minor groove of DNA by pyrrole-imidazole polyamides. *Chem. & Biol.* 4, 569-578 (1997); White, S., Baird, E. E. & Dervan, P.B. describes the 5'-3' N-C orientation preference for polyamide binding in the minor groove. New methods of designing selective compounds and the resulting specific polyamide binding ligands that are designed to target an identified sequence of double stranded DNA are needed to overcome the A•T/T•A degeneracy of pyrrole-imidazole polyamide recognition.

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